Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: A prospective, randomized trial

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Objective: Aortic surgical procedures requiring hypothermic circulatory arrest are associated with altered hemostasis and increased bleeding. In a randomized clinical trial, we evaluated effects of thromboelastometrically guided algorithm on transfusion requirements.

Methods: Fifty-six consecutive patients (25 with acute type A dissection) undergoing aortic surgery with hypothermic circulatory arrest were enrolled in a randomized trial during a 6-month period. Patients were randomly allocated to treatment group (n = 27) with thromboelastometrically guided transfusion algorithm or control group (n = 29) with routine transfusion practices (clinical judgment–guided transfusion followed by transfusion according to coagulation test results). Primary end point was cumulative allogeneic blood units (red blood cells, fresh-frozen plasma, and platelets) transfused.

Results: Transfusion of allogeneic blood was significantly reduced in the thromboelastometry group: median 9.0 units (interquartile range, 2.0–30.0 units) versus. 16.0 units (9.0–23.0 units, $P = .02$). Most significant decrease was in the use of fresh-frozen plasma (3.0 units, 0–12.0 units, vs 8.0 units, 4.0–18.0 units, $P = .005$). Postoperative blood loss (890 mL/d, 600–1250 mL/d vs 950 mL/d, 650–1400 mL/d, p = 0.5) and rate of surgical re-exploration (19% vs 24%, $P = .7$) were similar between groups. Thromboelastometrically guided algorithm significantly decreased need for massive perioperative transfusion (odds ratio, 0.45; 95% confidence interval, 0.2–0.9; $P = .03$) in multivariable logistic regression analysis.

Conclusions: Thromboelastometrically guided transfusion is associated with a decreased use of allogeneic blood units and reduced incidence of massive transfusion in patients undergoing aortic surgery with circulatory arrest. (J Thorac Cardiovasc Surg 2010;140:1117-24)

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Aortic surgical procedures requiring hypothermic circulatory arrest (HCA) are associated with altered hemostasis and increased bleeding.[1,2] Multiple factors have been reported to cause hemostatic derangements after aortic surgery, including surgical trauma, hypothermia, ischemia–reperfusion injury, extensive blood product and fluid requirements, activation of the systemic inflammatory response and fibrinolysis, and prolonged use of cardiopulmonary bypass (CPB).[3-7] These interactions can result in massive blood loss after aortic surgical procedures, which in turn is associated with an 8-fold increase in in-hospital mortality.[8] The multifactorial nature of coagulation disorders complicates clinical management, and treatment is often empirical.[9]

The positive effects of transfusion algorithms and point-of-care hemostasis testing on postoperative blood loss and transfusion requirements have been reported in several studies.[10-13] Reagent-modified rotational thromboelastometry (ROTEM) has an advantage of functional testing for specific defects in coagulation, all of which have specific treatment possibilities currently available to the practitioner. We wanted to determine whether a ROTEM-guided transfusion protocol would benefit patients undergoing high-risk aortic surgery. We therefore performed a monocentric, prospective study to compare transfusion requirements in patients undergoing aortic surgery with HCA and randomly allocated to receive either a ROTEM-guided transfusion protocol or standard clinical care.

MATERIALS AND METHODS

Patients

Approval for the study was obtained from the ethics committee of University Leipzig (Reg. No. 151-2007), and all patients gave written, informed consent. Eligible patients were those older than 18 years undergoing aortic surgery requiring HCA, including urgent and emergency surgery. Excluded patients were those who were pregnant, had known

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Abbreviations and Acronyms

ACT = activated clotting time
HCA = hypothermic circulatory arrest
ICU = intensive care unit
RBC = red blood cell
ROTEM = rotational thromboelastometry

(inherited) coagulation disorders (hemophilia A or B, activated protein C resistance, etc), or were unable to give informed consent. Patients receiving preoperative antiplatelet or anticoagulant therapy were eligible to participate. A total of 56 patients were entered into the trial between July 2007 and January 2008. Patients were randomly assigned with a computer-generated randomization list to either of 2 study groups: a control group (intraoperative transfusion guided by clinical judgment, followed by transfusion according to routine coagulation tests, n = 29) and a treatment group (ROTEM-guided transfusion algorithm, n = 27). Both transfusion algorithms are described in further detail (Tables 1 and 2). Random assignment was performed immediately on enrollment in the study.

Study End Points

The primary end point of the study was the cumulative number of allogeneic blood units (red blood cells [RBCs], fresh-frozen plasma, and platelets) transfused per patient. Secondary outcome measures were the use of prothrombin complex concentrate, fibrinogen concentrate, and recombinant factor VIIa (NovoSeven; Novo Nordisk A/S, Bagsværd, Denmark), blood losses in the first 12 and 24 postoperative hours, incidence of surgical re-exploration for bleeding, and related clinical outcome parameters (time to extubation, neurologic and renal complications, and stay in the intensive care unit [ICU]).

Intraoperative Management

Systemic full-dose heparin (300 units/kg) was administered as a bolus before cannulation for CPB. The activated clotting time (ACT) determined with Celite (Celite Corporation, Santa Barbara, Calif) was checked every 20 minutes during CPB, and additional heparin (5000 units) was given when the ACT was less than 450 seconds. Tranexamic acid was routinely used in both study arms according to a standardized protocol: 1 g intravenous infusion after anesthetic induction, 1 g intravenous infusion after skin incision, 1 g into the pump prime, and 1 g/h after discontinuation of CPB until the end of procedure.

CPB was instituted with right axillary perfusion and right atrial venous drainage. Systemic cooling was carried out with a maximal temperature gradient of 6°C. Directly before systemic perfusion was stopped, ice packs were placed around the head, and 100 mg dexamethasone was administered intravenously. Any aortic root procedure necessary was performed during the cooling phase. HCA was induced once the systemic temperature reached 23°C to 25°C rectally. Antegrade cerebral perfusion (10 mL/]kg · min]) was applied through perfusion of the axillary artery during clamping of the brachiocephalic trunk or direct cannulation of the supra-aortic vessels. Distal aortic repair was performed with an open technique during HCA. Perfusion was restored and rewarming was initiated thereafter, with a temperature gradient of less than 6°C. Rewarming was discontinued once the rectal temperature reached 36°C.

After discontinuation of CPB, reversal of heparin with a protamine ratio of 1:1 (1 mg \protamine per 100 units total heparin) was performed. An intraoperative cell-salvage device with reinfusion of shed mediastinal blood was used in all cases. No platelet-augmenting therapy, such as desmopressin acetate, was used. The only colloid used was 6% hydroxyethyl starch in a 130/0.4 solution.

TABLE 1. Transfusion protocol in the thromboelastometrically guided transfusion group

Finding	Response
CT by HEPTEM >260 s	FFP (15 mL/kg body mass)
CT by APTEM >120 s	3000 IU PPSB
MCF by HEPTEM 35–45 mm, MCF by FIBTEM >8 mm	1 platelet concentrate
MCF by HEPTEM <35 mm	1 platelet concentrate
MCF by FIBTEM <8 mm	2 g fibrinogen
MCF by APTEM/MCF by HEPTEM >1.5	3 g tranexamic acid
CT by INTEM/CT by HEPTEM >1.5 (in any post-CPB analysis)	5000 IU protamine

Protocol lists actions taken in response to findings of 4-channel rotational thromboelastometric analysis at 32°C rectally. *CT,* Coagulation time; *HEPTEM,* intrinsic activation plus heparinase neutralization thromboelastometry; *FFP,* fresh-frozen plasma; *APTEM;* extrinsic activation plus aprotinin thromboelastometry; *PPSB,* prothrombin complex concentrate; *MCF,* maximal clot firmness; *FIBTEM,* fibrinogen-based extrinsic activation thromboelastometry; *INTEM,* intrinsic activation thromboelastometry; *CPB,* cardiopulmonary bypass.

Triggers for RBC transfusion were identical in both study arms: a minimum hematocrit of 20% (hemoglobin 6.8 g/dL) during CPB and a minimum hematocrit of 25% (hemoglobin 8.5 g/dL) after CPB. RBCs were occasionally transfused despite hematocrit levels greater than 25% when physiologic transfusion triggers occurred: hemodynamic instability (epinephrine or norepinephrine >10 μg/[kg · min]), signs of myocardial ischemia on electrocardiography, or drop in mixed venous oxygen saturation below 50% (central venous oxygen saturation below 60%). Mixed venous oxygen saturation was measured with a pulmonary artery catheter only in patients who required high-dose catecholamine support (epinephrine or norepinephrine, >10 μg/[kg · min]) to wean them from CPB or who had low cardiac output later in the ICU. The remaining patients were monitored with only central venous oxygen saturation measurements.

Hemostatic Management

ROTEM group. Intraoperative and postoperative transfusions of blood products were guided by a ROTEM-based protocol (Table 1). Reagent-modified 4-channel rotational thromboelastometry with ROTEM coagulation analyzer (Matel Medizintechnik GmbH, Munich, Germany) was implemented to screen for coagulation disorders. The basic principles of ROTEM have been previously described in multiple studies.[14-18] Briefly, the original thrombelastometric procedure has been modified by providing computerized analysis of the trace and by adding different coagulation-accelerating agents to make the analysis more expeditious and to allow the detection of specific coagulation defects (factor deficiency, presence of heparin, fibrinogen deficiency, platelet deficiency, and hyperfibrinolysis).

TABLE 2. Transfusion protocol in the control group

Finding	Response
Activated clotting time >160 s	5000 IU protamine (1 time)
Partial thromboplastin time >60 s or INR >1.5	FFP (15 mL/kg body mass)*
Platelets <100,000 cells/μL	1 platelet concentrate
Fibrinogen <1.2 mg/dL	2 g fibrinogen
α_2-Antiplasmin <80%	3 g tranexamic acid

Protocol lists actions taken in response to results of standard coagulation tests (platelet count, international normalized ratio, partial thromboplastin time, fibrinogen, α_2-antiplasmin, activated clotting time, antithrombin III) after protamine administration. *FFP,* Fresh-frozen plasma; *INR,* international normalized ratio. *Give 3000 IU prothrombin complex concentrate only if international normalized ratio greater than 2.0 along with known liver dysfunction or warfarin therapy.

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The 2 treatment-relevant parameters of the ROTEM trace (used in this study) are clotting time, which allows the analysis of coagulation factor deficiency or presence of anticoagulants, and maximal clot firmness, which gives information about fibrinogen and platelets (Figure E1). A baseline test (INTEM) uses a contact activator to analyze the general coagulation status related to intrinsic factors. In a simultaneously performed intrinsic clotting test with added heparinase (HEPTEM), residual heparin can be demonstrated. In a test of extrinsic factors (FIBTEM), cytochalasin D is used as a platelet inhibitor, allowing the analysis of fibrinogen effect on maximal clot firmness alone. In another test of extrinsic factors (APTEM), tissue factor and aprotinin are used to identify hyperfibrinolysis. The 4 measurement channels of the ROTEM device allow performance of all 4 tests simultaneously with a single analyzer run.

Initial ROTEM analysis was performed at 32°C during the rewarming phase of CPB. Test results were available for operating room personnel before to the beginning of weaning from CPB, approximately 20 to 25 minutes after blood sampling. The required blood products were ordered according to the appropriate transfusion protocol (Table 1) and administered simultaneously with protamine infusion after discontinuation of CPB. The extent of microvascular bleeding was assessed subjectively by the attending surgeon as the absence of visible clots in the surgical field 15 minutes after administration of blood products. The second ROTEM analysis was carried out for documentation of transfusion effect, irrespective of bleeding. If no microvascular bleeding was determined, the chest was closed, and further ROTEM tests were performed in the ICU only in case of increased bleeding (>200 mL in the first hour or >100 mL/h thereafter). Further blood products were given according to the results of ROTEM analysis. In cases of persistent microvascular bleeding in the operating room, ROTEM coagulation analysis was performed 15 minutes after administration of all appropriate coagulation products, and new blood products were ordered according to the results of the most recent analysis.

Control group. Patients in the control group received the initial transfusion in the operating room on the basis of clinical judgment (empirically) and subsequently on the basis of standard coagulation test results (Table 2). This protocol was the same as that we had previously used for routine clinical practice in patients undergoing aortic surgery with HCA. After discontinuation of CPB, protamine was administered simultaneously with other blood products, as the attending anesthesiologist and operating surgeon deemed them necessary. One additional dose of protamine (50 mg) was given if the postprotamine ACT had not returned to within 15% of the preheparin value. Blood samples for laboratory tests were drawn thereafter. If no abnormal bleeding was observed, the chest was closed, and further transfusion was performed only in case of increased bleeding in the ICU (>200 mL in the first hour or >100 mL/h thereafter), according to the algorithm based on coagulation test results (Table 2). In cases of persistent oozing with no visible clots in the operating field, further blood products were administered on an empirical basis until coagulation test results were available. An interval of approximately 60 minutes was required to receive the results from the laboratory.

Management in the ICU. Surgical re-exploration was performed if bleeding persisted despite normal ROTEM analysis (ROTEM group) or coagulation test results (control group), if bleeding was excessive (> 400 mL/h), or if signs of cardiac tamponade occurred. The criteria for surgical re-exploration were identical in both study arms. The decision for off-label use of recombinant factor VIIa (NovoSeven) was made if the bleeding persisted after resternotomy without any identifiable surgical bleeding source. A dose of 80 μg/kg was administered, irrespective of group affiliation.

Statistical Analysis

Power analysis was based on our initial experience with the ROTEM analyzer and the results from previous studies with thromboelastometrically guided algorithms in cardiac surgery.[16,18] Power analysis suggested that 30 patients per group would be required to demonstrate a 40% reduction in the use of allogeneic blood products at an α of 0.05 and a power of 80%.

Categoric variables are expressed as percentages, and continuous variables are expressed as mean ± SD or as median with 25th and 75th percentiles (interquartile range) throughout this article. All statistical analyses were performed with the SPSS version 14.0 software package (SPSS Inc, an IBM Company, Chicago, Ill). Continuous variables were analyzed with the unpaired 2-tailed Student *t* test (after confirmation of normal distribution and homogeneity of variance by the Levene test) or with the Mann–Whitney *U* test for nonnormally distributed variables. Fisher's Exact test was applied to all categoric variables. All comparisons were made on an intention-to-treat basis. Logistic regression analysis was used to identify predictors of massive transfusion (>20 units of allogeneic blood).

RESULTS

A total of 56 consecutive patients were enrolled in the study during a period of 6 months (from July 2007 to January 2008). Nearly all patients (33 of 35) undergoing elective aortic surgery with HCA during the study period were enrolled. Two elective patients were not recruited because of technical problems with the ROTEM analyzer at the time of surgery. The decision to perform HCA was made intraoperatively (was not planned on the basis of preoperative evaluation) in another 3 elective cases during the study period and these patients were not included in the study. A total of 31 patients with acute type A dissection were operated on during the study period, and 25 of them (81%) were included in this study. The reasons for nonenrollment in this subgroup were critical patient status (written, informed consent could not been obtained) in 4 cases and nonavailability of the study personnel in the remaining 2 cases.

A total of 98 thromboelastometric analyses were performed in the ROTEM group (3.6 tests/patient). Divergences from the treatment algorithm were required in 4 patients (15%) in the ROTEM group and 2 patients (7%) in the control group. Two patients with acute type A dissection in the ROTEM group had persistent microvascular bleeding after the first administration of blood products according to the ROTEM protocol, and further blood products were ordered empirically on preference of the operating surgeon. The third patient had a massive blood loss caused by intraoperative dissection of the descending thoracic aorta and underwent empirical transfusion therapy in the operating room. One elective patient in ROTEM group underwent empirical transfusion because of the unavailability of ROTEM analysis results after discontinuation of CPB (ROTEM analysis had to be repeated because of inadequacy of the first sample). Both treatment divergence patients in the control group were operated on for acute type A dissection and required use of recombinant factor VIIa because of persistent microvascular bleeding, despite numerous empirical blood product transfusions. The results from all 6 patients were included on an intention-to-treat basis.

The 2 groups were similar with regard to preoperative characteristics. In particular, the proportion of patients presenting with acute dissection was not different between groups (41% vs 48%, $P = .6$; Table 3). There were no

TABLE 3. Preoperative variables

Variable	ROTEM (N = 27)	Control (N = 29)	*P* value
Age (y, mean ± SD)	63.5 ± 13.5	59.9 ± 17.5	.3
Male (no.)	15 (56%)	17 (59%)	.8
Body mass index (kg/m^2, mean ± SD)	27.1 ± 8.0	27.4 ± 4.5	.9
Arterial hypertension (no.)	22 (82%)	22 (76%)	.7
Left ventricular ejection fraction (%, mean ± SD)	57.2% ± 11.6%	62.7% ± 13.5%	.2
Peripheral arterial disease (no.)	1 (4%)	1 (4%)	.9
Chronic obstructive pulmonary disease (no.)	4 (15%)	3 (10%)	.6
Liver dysfunction (no.)	1 (4%)	2 (7%)	.7
Diabetes mellitus (no.)	4 (15%)	3 (10%)	.6
Preoperative creatinine (mg/dL, mean ± SD)	0.9 ± 0.3	1.1 ± 0.4	.2
Preoperative shock (no.)	1 (4%)	1 (4%)	.9
Acute type A aortic dissection (no.)	11 (41%)	14 (48%)	.6
Chronic aortic dissection (no.)	4 (15%)	5 (17%)	.8
Nondissecting aortic aneurysm (no.)	12 (44%)	10 (35%)	.5
Marfan syndrome (no.)	4 (15%)	4 (14%)	.9
Previous cardiac surgery (no.)	5 (19%)	7 (24%)	.7
Preoperative aspirin (no.)	9 (33%)	8 (28%)	.5
Preoperative warfarin (no.)	1 (4%)	1 (4%)	.9
Preoperative hematocrit (%, mean ± SD)	38.0% ± 5.0%	36.9% ± 6.5%	.6
Preoperative hemoglobin (g/dL, mean ± SD)	12.6 ± 1.9	12.2 ± 2.5	.6
Platelet count (cells/μL, mean ± SD)	220 ± 90	245 ± 110	.6
International normalized ratio (mean ± SD)	1.3 ± 0.6	1.1 ± 0.4	.8
Partial thromboplastin time (s, mean ± SD)	37 ± 14	39 ± 11	.8
Fibrinogen (mg/dL, mean ± SD)	2.2 ± 1.7	2.4 ± 2.0	.9
α_2-Antiplasmin (%, mean ± SD)	92% ± 7.0%	94% ± 9.5%	.8
Activated clotting time (s, mean ± SD)	145 ± 90	136 ± 80	.6
Logistic EuroSCORE (%, mean ± SD)	30.7% ± 20.3%	28.6% ± 16.6%	.7

ROTEM, Thromboelastometry.

major differences in the use of aspirin and warfarin before surgery, and none of the patients were receiving preoperative clopidogrel or heparin. A total of 79% of patients in the control group and 82% of patients in the ROTEM group ($P = .8$) were classified as having high-risk score for massive perioperative transfusion, according to the published transfusion risk scores.[19,20]

The details of intraoperative management are displayed in Table 4. The extent of surgical procedure was comparable between the groups, although there was a trend toward slightly longer CPB and aortic crossclamp times, as well as higher incidence of aortic root replacement, in the control group. None of these differences, however, reached statistical significance.

The primary and secondary outcomes are displayed in Table 5. The cumulative use of allogeneic blood units was reduced by 44% in the ROTEM group relative to the control group (9.0 units, 2.0–30.0 units, vs 16.0 units, 9.0–23.0 units, $P = .02$). The most significant decrease was achieved in the use of fresh-frozen plasma. Although there was a significant difference in RBC transfusion between the groups until 24 hours postoperatively (Figure E2), there was only a trend toward a reduced cumulative RBC transfusion for the whole hospital stay (Table 5). The transfusion requirements for platelets and fibrinogen concentrate were comparable between groups. The use of prothrombin complex concentrate was significantly reduced in the ROTEM-guided group (Table 5). Recombinant factor VIIa was used in 1 patient (4%) in the ROTEM group versus 2 patients (7%) in the control group ($P = .8$).

Blood losses in the first 12 and 24 postoperative hours and the need for surgical re-exploration for bleeding were similar between groups. A surgical bleeding source was identified in most of the re-explored patients (80% of re-explored patients in the ROTEM group vs 71% in the control group).

Hemoglobin levels were comparable between the groups throughout the postoperative course: 9.4 ± 1.5 g/dL in the ROTEM group versus 9.2 ± 0.9 g/dL in the control group ($P = .7$) at arrival in the ICU, 9.6 ± 0.6 g/dL in the ROTEM group versus 9.1 ± 0.7 g/dL in the control group ($P = .4$) at 24 postoperative hours, and 10.7 ± 2.3 g/dL in the ROTEM group versus 10.3 ± 1.6 g/dL in the control group ($P = .6$) at discharge from the hospital.

Clinical outcome variables were comparable between groups. In particular, there were no differences in the incidences of respiratory insufficiency, neurologic complications, and dialysis-dependent renal failure. Accordingly, the ICU stay, hospital stay, and in-hospital mortality were similar between groups (Table E1).

TABLE 4. Intraoperative variables

Variable	ROTEM (N = 27)	Control (N = 29)	*P* value
Axillary arterial perfusion (no.)	18 (67%)	20 (69%)	.8
Cardiopulmonary bypass (min, mean ± SD)	196.5 ± 50	208 ± 52	.3
Aortic crossclamp (min, mean ± SD)	101.7 ± 22	115.9 ± 37	.2
Circulatory arrest (min, mean ± SD)	22.3 ± 18	25.8 ± 23	.5
Minimal temperature (°C, mean ± SD)	24.5 ± 1.6	24.8 ± 3.5	.8
Antegrade cerebral perfusion (no.)	22 (82%)	23 (79%)	.8
Aortic root replacement (no.)	11 (41%)	16 (55%)	.1
Aortic root reconstruction (no.)	12 (44%)	9 (31%)	.2
Hemiarch replacement (no.)	16 (59%)	15 (52%)	.5
Total arch replacement (no.)	10 (37%)	12 (41%)	.8
Concomitant coronary artery bypass grafting (No.)	3 (11%)	4 (14%)	.8

ROTEM, Thromboelastometry.

In a subgroup analysis of 16 elective patients in the ROTEM group, 4 patients did not need any blood products transfused. None of the patients in the control group avoided allogeneic blood transfusion. Four patients with divergences from the transfusion protocol in the ROTEM group required massive perioperative transfusion (a total of 114 allogeneic blood units, 38% of all units used in the ROTEM group).

We conducted a logistic regression analysis to identify the predictors of massive transfusion (>20 allogeneic blood units). A total of 9 clinically relevant variables were included in the multivariate model, and the ROTEM-guided algorithm was found to be protective against massive allogeneic blood product transfusion (odds ratio 0.45, $P = .03$; Table E2).

DISCUSSION

Several studies have advocated the benefits of ROTEM-guided algorithms in terms of transfusion reduction in cardiac surgical patients.[17,18] Most of these studies, however, have included elective coronary and valve surgical patients at low or medium risk for perioperative bleeding.[17,18,21,22] Therefore little is known about ROTEM-guided coagulation management in cardiac surgical patients at high risk for excessive bleeding. A review of the literature revealed a single study that specifically addressed ROTEM-guided transfusion in pediatric cardiac surgical patients undergoing HCA (n = 10).[23] To the best of our knowledge, a ROTEM-guided transfusion protocol has not been specifically evaluated in adult patients undergoing aortic surgery with HCA.

We performed a randomized trial comparing the effects of ROTEM-guided coagulation management with those of standard clinical care in patients undergoing aortic surgery with HCA. We assumed that the major benefit of heparinase-modified ROTEM would be an early identification of coagulation abnormalities during the rewarming phase of CPB, with subsequent administration of required blood components (according to the ROTEM protocol) simultaneously with protamine infusion.[24] We anticipated that this approach would save the maximum amount of time, reduce the amount of shed mediastinal blood

TABLE 5. Perioperative transfusion and blood loss

Variable	ROTEM (N = 27)	Control (N = 29)	*P* value
RBCs (units, median and IQR)	6.0 (2.0–13.0)	9.0 (4.0–14.0)	.2
Patients transfused with RBCs (no.)	24 (89%)	27 (93%)	.8
FFP (units, median and IQR)	3.0 (0–12.0)	8.0 (4.0–18.0)	.01
Patients transfused with FFP (no.)	9 (33%)	25 (86%)	<.001
Platelet concentrate (units, median and IQR)	1.0 (0–4.0)	2.0 (1.0–3.0)	.7
Patients transfused with platelets (no.)	14 (52%)	23 (79%)	.03
Allogeneic blood units (cumulative, median and IQR)	9.0 (2.0–30.0)	16.0 (9.0-23.0)	.02
Patients transfused with allogeneic blood (no.)	24 (89%)	29 (100%)	.06
PCC (IU, median and IQR)	0 (0–2000)	3000 (2000–3000)	<.001
Patients transfused with PCC (no.)	4 (15%)	26 (90%)	<.001
Fibrinogen concentrate (g, median and IQR)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	.7
Patients transfused with fibrinogen (no.)	21 (78%)	26 (90%)	.2
Patients with massive transfusion (>20 units, no.)	5 (19%)	10 (35%)	.1
Blood loss in 12 h (mL, median and IQR)	600 (380–950)	680 (450–1000)	.3
Blood loss in 24 h (mL, median and IQR)	890 (600–1250)	950 (650–1400)	.5
Re-exploration for bleeding (no.)	5 (19%)	7 (24%)	.7
Non-RBC fluid balance in OR (mL, median and IQR)	1800 (1200–2200)	1600 (1100–2000)	.7
24-h non-RBC fluid balance (mL, median and IQR)	2600 (1700–2900)	2500 (1500–3000)	.8
Total heparin dose (IU, median and IQR)	38,000 (32,000–43,000)	39,000 (34,000–46,000)	.8
Total protamine dose (IU, median and IQR)	41,000 (34,000–46,000)	43,000 (35,000–49,000)	.6
Use of factor VIIa (no.)	1 (4%)	2 (7%)	.8

ROTEM, Thromboelastometry; *RBC,* red blood cell; *IQR,* interquartile range; *FFP,* fresh-frozen plasma; *PCC,* prothrombin complex concentrate.

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reinfused, and stop the progression of coagulopathy at a very early stage.

The main finding of this study is that a significant reduction in allogeneic blood transfusion was achieved by means of a ROTEM-guided algorithm in patients undergoing aortic surgery with HCA. In addition, ROTEM-guided coagulation management was associated with a decreased risk of massive transfusion, after adjustment for other important transfusion risk factors (Table E2).

The observed cumulative decrease in allogeneic blood unit use of 44% in the ROTEM group is in accordance with the results of a previous randomized trial involving cardiac surgical patients at low or medium risk for excessive bleeding.[24] We observed the most significant reduction in the use of fresh-frozen plasma, which was decreased by 62% in the ROTEM group. Similar evidence comes from another randomized trial in which the decrease in use of allogeneic blood products in the thrombelastometry group was predominantly caused by a reduced need for fresh-frozen plasma transfusion.[21]

In contrast, fibrinogen deficiency was one of the most common findings of our ROTEM analyses. The key role of fibrinogen substitution in major surgical bleeding has been stressed in several previous publications.[25]

The use of RBC units in the ROTEM group showed a 33% decrease relative to that in the control group, although this difference did not reach statistical significance. Other investigators have reported similar findings,[18] although some groups have found a statistically significant reduction in RBC transfusions in their thromboelastometrically guided transfusion groups.[17,21] The prolonged and complicated postoperative courses of more than 20% of the high-risk patients in our study necessitated transfusion of additional RBC units later, during the ICU or intermediate care unit stay. These late transfusions mitigated the initially statistically significant difference (Figure E2) between the study groups. Moreover, the protocol violations in the cases of 4 patients in the ROTEM-guided group who underwent empirical blood product therapy and subsequently required massive transfusion (accounting for 38% of the allogeneic blood units used in the ROTEM group) may have further reduced the difference in RBC use between the study groups.

The second most common finding in our ROTEM analyses was quantitative or qualitative platelet deficiency. Although the proportion of patients requiring transfusion of platelet concentrates was significantly lower in the ROTEM group, the cumulative number of platelet concentrate units transfused was not different between groups (Table 5). In contrast, other thromboelastometrically guided transfusion studies have reported a significant reduction in cumulative number of platelet concentrate units transfused.[17,18,21] This discrepancy could be explained by differences between our ROTEM algorithm and the algorithms used in the other studies. Alternatively, our lack of difference in platelet transfusion between study groups may have been due to the known high incidence of platelet dysfunction in this high-risk cohort of aortic surgical patients.

Because of the aggressive intraoperative antifibrinolytic drug regimen routinely used at our institution,[26] the need for additional tranexamic acid was negligible. Only 1 patient in the ROTEM group and 2 in the control group required additional tranexamic acid.

The major finding of this study was a significant reduction in fresh-frozen plasma transfusion in the ROTEM-directed group. It may be postulated that similar results could have been achieved by simply reducing fresh-frozen plasma administration in the empirical transfusion control group. Indeed, some experts have suggested limiting fresh-frozen plasma transfusions during high-risk cardiac surgery.[27] Although judicious empirical blood product transfusion may sufficiently meet transfusion requirements in most high-risk cases, ROTEM may still be helpful for patients with persistent microvascular bleeding by providing a quick assessment of the entire coagulation system. Moreover, there may be advantages of the ROTEM-directed protocol that were not elucidated by the primary end point of our study. For example, we were able to eliminate almost completely the use of prothrombin complex concentrate, a cost-intensive product, in the ROTEM group. We may also conclude from our study that transfusion requirements are highly variable between patients. For example, 15% of patients in the ROTEM group did not require any blood transfusion throughout the entire perioperative and postoperative course.

Despite the significant reduction in allogeneic blood units used in the ROTEM-group, no increased postoperative blood loss and no increased rate of re-exploration for postoperative bleeding or tamponade was observed in ROTEM-guided group (Table 5). This finding has been supported by the results of other randomized thromboelastometric trials.[21,24] High re-exploration rates in both study arms (19% and 24%) may be explained by high proportion of patients with an acute type A dissection in this study, as well as by rigorous re-exploration strategy. Re-exploration was performed expeditiously if results of coagulation tests (control group) or ROTEM analysis (ROTEM group) were normal, not waiting until the chest tube drainage had reached any predefined levels. This is based on a good predictive value of ROTEM for detection of surgical bleeding, as demonstrated by Cammerer and colleagues.[22] In our study, 4 patients in the ROTEM group who underwent re-exploration for bleeding had normal ROTEM results, and a surgical bleeding source was found in all cases. If bleeding persists in the ICU despite a normal ROTEM, it is thus very likely that this bleeding is surgical in nature. Because the results of ROTEM analysis are available within 15 minutes, the decision as to whether to take a patient back to the operating room can be made more expeditiously.

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Although this result was somewhat disappointing, we could not find any significant difference in the clinical variables between the study arms (Table E1). There could be several explanations for this finding. First, the blood loss and transfusion requirements during aortic surgery with HCA (especially acute dissection surgery) are substantial, even when ROTEM-guided therapy is used (median blood loss 890 mL/24 h [600–1250 mL]), and median allogeneic blood used per ROTEM patient in this study 9.0 units (2.0–30.0 units). Thus even a 44% reduction in allogeneic blood transfusions may not have been large enough to alleviate transfusion-related postoperative events. Second, postoperative complications after aortic surgery are likely multifactorial, and transfusion-related events may be seen as only a contributing factor to these complications. Third, and most importantly, our study was underpowered to detect differences in these secondary clinical outcome variables.

We found it very important to have experienced personnel available on a 24-hour basis in the ICU to perform the ROTEM tests, because the use and interpretation of the ROTEM analyzer can be technically challenging. This was the reason for nonenrollment of 2 elective patients and for the divergence from ROTEM-guided algorithm in 1 other case.

Study Limitations

There are several limitations of this study. Because of the well-known bleeding tendency in this high-risk patient population, our study protocol was designed to administer the required blood products (in both study groups) simultaneously with protamine infusion after discontinuation of CPB. The bias may play a role when nonblinded control group patients were treated empirically (that is, control group patients were transfused on the basis of clinical discretion at first), whereas ROTEM-guided patients received the blood products solely on the basis of test results. This is consistent with the clinical routine, however, because the coagulation test results are usually not available in the immediate postprotamine period. Transfusion therapy is thus directed empirically at first to counteract the excessive blood loss that is often encountered in these cases. This fact underscores the advantage of ROTEM analysis, because the test results are available before the start of weaning from CPB. Nonetheless, we are aware that any special therapy we implement to reduce transfusions will exert a positive effect just by establishing a strict protocol.

We acknowledge that routine coagulation tests may be more effective than they were in this study, provided the time to obtain these results is shorter than in our institution. These laboratory parameters did not really represent the hemostatic situation by the time they were available. The long delay for the coagulation test results may have negatively influenced the results in the control group. The major advantage of ROTEM is that all key parameters to guide the transfusion are available within 15 minutes.

Divergences from the transfusion protocol were required for 4 patients (15%) in the ROTEM group, all of whom subsequently had excessive blood loss and required massive transfusion. This undoubtedly weakened the positive results in the ROTEM group and may explain to some extent the lack of differences in the blood loss and in the rate of reexploration between the groups (Table 5). Most of these protocol violations occurred in the early stage of this study. These divergences became very rare as we gained more experience with ROTEM.

In this study, we attempted to make our results generalizable to this high-risk patient population by recruiting the vast majority of consecutive aortic surgical patients operated on during the study period, including the majority of patients undergoing emergency surgery (81% of acute type A dissections), as well as patients receiving preoperative antiplatelet or warfarin therapy. Inclusion of emergency cases in the study raises the problem of introducing some poorly controlled variables. Nonetheless, these are the patients who are at extremely high risk for excessive bleeding, and they are expected to benefit most from the fast and reliable guidance of perioperative transfusion.

In addition, heparinase-modified ROTEM may overestimate the level of coagulopathy (especially platelet dysfunction) during CPB, provoking unnecessary transfusion. This may be among the explanations for the lack of difference in platelet transfusion between the groups.

CONCLUSIONS

In conclusion, this randomized trial demonstrated that the use of a ROTEM-guided transfusion algorithm in aortic surgical patients undergoing HCA was associated with a significant decrease in the cumulative number of transfused allogeneic blood units. This reduction was predominantly caused by the reduced need for fresh-frozen plasma transfusion. ROTEM usage was also independently associated with a reduced risk of massive perioperative transfusion in these high-risk patients. ROTEM-guided coagulation management should be considered for all cardiac surgical patients who are at high risk for perioperative bleeding.

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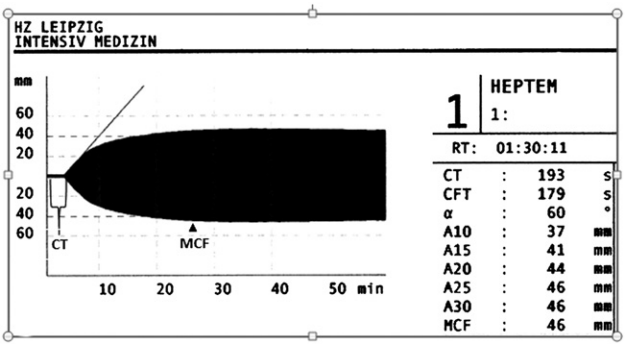

FIGURE E1. Typical rotational thromboelastometric trace (ROTEM; Matel Medizintechnik GmbH, Munich, Germany) with key parameters. *HEPTEM*, Intrinsic activation plus heparinase neutralization thromboelastometry; *RT,* time when the ROTEM-analysis has been performed; *CT,* clotting time; *CFT,* clot formation time; *α,* alpha angle; *MCF,* maximal clot firmness; *A10, A15, A20, A25, A30,* clot firmness (amplitude) at 10, 15, 20, 25, and 30 minutes, respectively.

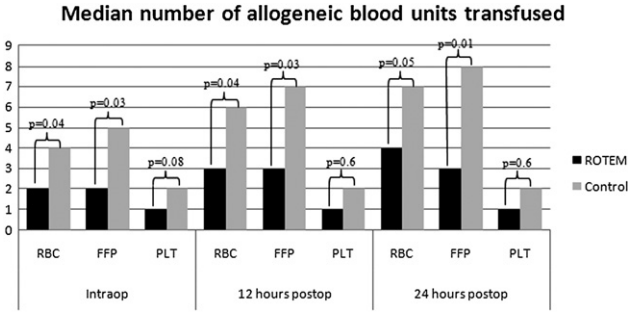

FIGURE E2. Allogeneic blood units transfused during first 24 postoperative hours. *ROTEM,* Rotational thromboelastometrically guided protocol; *RBC,* red blood cell; *FFP,* fresh-frozen plasma; *PLT,* platelet concentrate; *Intraop,* intraoperative*; postop,* postoperative.

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TABLE E1. Clinical outcome variables

Variable	ROTEM (N = 27)	Control (N = 29)	*P* value
Time to first extubation (h, mean ± SD)	127 ± 135	113 ± 154	.7
Reintubation (no.)	7 (26%)	5 (17%)	.4
Total ventilation time (h, mean ± SD)	144 ± 139	137 ± 172	.8
Stroke (no.)	4 (15%)	3 (10%)	.6
Postoperative confusion (no.)	4 (15%)	7 (24%)	.5
Dialysis-dependent renal failure (no.)	5 (19%)	7 (24%)	.6
Intensive care unit stay (d, mean ± SD)	7.3 ± 9.1	8.1 ± 8.4	.6
Intensive care unit stay >10 d (no.)	6 (22%)	7 (24%)	.8
Hospital stay (d, mean ± SD)	16.6 ± 16.4	17.0 ± 14.8	.8
In-hospital mortality (no.)	4 (15%)	5 (17%)	.8

ROTEM, Thromboelastometry.

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TABLE E2. Multivariate analysis of massive blood transfusion (>20 units)

Variable	OR	95% CI	*P* value
Thromboelastometrically guided protocol	0.45	0.2–0.9	0.03
Age >70 y	1.1	0.3–7.8	0.8
Preoperative aspirin	1.9	0.5–8.5	0.5
Circulatory arrest >30 min	2.6	0.7–11.5	0.3
Reoperation	3.4	0.6–17.8	0.3
Acute type A dissection	3.9	1.9–11.7	0.03
Preoperative creatinine >1.5 mg/dL	6.2	0.9–15.2	0.1
Cardiopulmonary bypass time >200 min	7.9	1.2–35.1	0.03
Preoperative hematocrit <30%	15.1	1.9–65.3	0.02

OR, Odds ratio; *CI,* confidence interval.